Remarks

Claims 28, 57 and 62-65 were previously pending in the subject application. By this Amendment, the applicants have cancelled claim 65. Accordingly, claims 28, 57 and 62-64 are before the Examiner for his consideration.

Initially, the applicants would like to thank the Examiner for the confirmation that the Terminal Disclaimer filed on 10 June 2005 has been reviewed and accepted, and that the double patenting rejection has been withdrawn.

The applicants also wish to express their appreciation for the Examiner's indication that the prior art rejections based on Lamarco *et al.*, Jamieson *et al.*, Desjarlis *et al.*, and Krizek *et al.* have now been withdrawn.

Claims 28, 57 and 62-65 have been rejected under 35 U.S.C. §112, first paragraph. The applicants respectfully traverse this ground for rejection because the specification, as filed, provides ample guidance to enable the skilled practitioners to make and use the subject invention as claimed.

In making the rejection under 35 U.S.C. §112 the Office Action cites *In re Wands.* The applicants appreciate the Examiner's analysis of the "Wands factors" and have addressed these factors in detail below. Initially, however, it is important to note that enablement does not require the applicant to teach what is already known or to provide excruciating detail of every step that is to be carried out to practice the invention. Furthermore, some level of experimentation in the practice of the invention is perfectly acceptable. In fact the *Wands* case cited in the Office Action specifically states as follows:

> Enablement is not precluded by the necessity for some experimentation such as routine screening. . . A considerable amount of experimentation is permissible, if it is merely routine . . . *In re Wands*, 8 USPQ 2d 1400, 1404 (Fed. Cir. 1988).

As discussed in more detail below, the current applicants provide in the specification ample guidance for making and using TBAs as claimed. Furthermore, a review of the biology of phages as well as post-filing date scientific articles by independent third parties confirms the utility and enablement of the current invention.

Following is analysis of the "Wands factors" cited in the outstanding Office Action. The applicants respectfully submit that a careful analysis of these factors leads to the conclusion that the invention as claimed in the current application is fully enabled because the highly skilled artisan in this field could readily make and use the TBAs as described without undue experimentation.

First, with regard to the amount of experimentation needed to practice the invention, the applicants respectfully submit that any such experimentation would be routine for those skilled in the art. Certainly it is straightforward to construct TBAs and administer them to cells. Furthermore, given the guidance provided by the applicants, a high expectation of achieving the desired binding characteristics would exist.

As noted above, it is well settled that valid patent claims may still require the skilled artisan to perform some amount of experimentation in order to determine the preferred way to apply an invention to a particular situation. See, for example, Fields v. Conover, 443 F.2d 1386, 1390-91, 170 USPQ 276 (CCPA 1971) ("[A] disclosure complies with [§112] even though `some experimentation, provided it is not an undue amount' [and provided that it does not require ingenuity beyond that to be expected of one of ordinary skill in the art] is still required to adapt the invention to particular settings."; Douglas v. United States, 510 F.2d 364, 366, 184 USPQ 613 (Ct. Cl. 1975), *cert. denied*, 423 U.S. 825 (1975) ("Nor can a patentee be expected to foresee every technological problem that may be encountered in adapting his idea to a particular use. Some experimentation and exercise of judgment is to be expected"); Wilden Pump & Eng'r Co. v. Pressed & Welded Pod. Co., 199 USPQ 390 (N.D. Cal. 1978), *aff'd*, 655 F.2d 984, 213 USPQ 282 (9th Cir. 1981), *on remand*, 570 F. Supp. 224, 224 USPQ 1074 )N.D. Calif. 1983) ("A patent's disclosure is adequate if it defines the desired functional relationship, even if some experimentation is required to reproduce the invention."); *In re* Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (U.S. Int'l Trade Comm. 1983), *aff'd sub mom.*, Massachusetts Institute of Technology V. AB Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985) ("[T]he fact that experimentation may be complex . . . does not necessarily make it undue, if the art typically engages in such experimentation."). Given the teachings of the subject application, it would be a straightforward matter for the skilled practitioner to use the TBA to achieve the desired effect.

Thus, with regard to *Wands* factor (a), the applicants respectfully submit that there would not be much experimentation needed and, in any event, the experimentation would be routine given the level of skill in the art and the guidance provided in the subject application.

With regard to *Wands factor* (b), the outstanding Office Action states as follows:

> b) The specification provides general guidance for therapeutic or prophylactic use of TBAs in HIV infected patients on pages 40-41 and 59-60 without providing specific guidance that shows how to deliver sufficient levels of the TBA to all infected cells in the patient to eliminate an HIV infection or to eliminate symptoms of an HIV infection. The specification does not provide guidance to treat any disease other than HIV infections.

With regard to this issue, the applicants respectfully submit that the claims do not require administration to "all" cells or the elimination of the infection. As for other diseases, HPV is also recited and there is no reason to believe the teachings of these pathogens could not be applied to others.

With regard to (c), the applicants respectfully note that the application provides numerous specific examples of sequences that can be used according to the subject invention. Furthermore, a person following the teachings of the specification could practice the invention without undue experimentation, no more is required by §112.

With regard to the nature of the invention (*Wands Factor* (d)), although gene expression is complex, making and using TBAs as described by the current applicants is relatively straightforward with, as described herein, high expectations of achieving the desired binding characteristics.

With regards to *Wands factor* (e), the Office Action refers to various articles that outline certain challenges associated with the use of zinc fingers, antisense polynucleotides and ribozymes. However, even if these related technologies require further work for optimization, this does not negate the fact that the skilled artisan could make and use the claimed TBAs as described and claimed by the current applicant.

Moreover, it is well established through case law "that it is not difficult matter to carry out a process in such a fashion that it would not be successful and, therefore, the failures of experiments

who have no interest in succeeding should not be according great weight", see *In re Michalek*, 74 USPQ 108, at 109 citing *Bullard Company et al. v. Coe*, 147 F.2d. 568, 64, USPQ 359.

Furthermore, court decisions clearly hold that 35 U.S.C. 112, first paragraph, does not require every embodiment within the scope of a given claim to have the same utility or even to be operable. Therefore, the possibility that some inoperative embodiments may exist does not negate patentability. See, for example, Syntex (U.S.A.) Inc. v. Paragon Optical Inc., 7 USPQ2d 1001, 1035 (D. Ariz. 1987) ("Patent claims that included some claimed combinations which are inoperative are not necessarily invalid under 35 U.S.C. 2 §112 . . . It is impractical and unreasonable to require a patentee to set out an extended list of precise combinations and formulae since one skilled in the art would avoid obvious inoperative combinations."); Hybritech, Inc. v. Abbott Laboratories, 4 USPQ2d 1001, 1012 (C.D. Calif. 1987), *aff'd*, 849 F.2d 1446, 7 USPQ2d 1191 (Fed. Cir. 1988) ("the existence of one nonoperational embodiment within the scope of a claim does not invalidate the patent"); Horton v. Stevens, 7 USPQ2d 1245, 1247 (Bd. Pat. App. & Int'f 1988) ("The mere fact that a claim embraces undisclosed or inoperative species or embodiments does not necessarily render it unduly broad."); Shields v. Halliburton Co., 493 F. Supp. 1376, 207 USPQ 304 (W.D. La. 1980), *aff'd*, 667 F.2d 1232, 216 USPQ 1066 (5th Cir. 1982) ("Subject matter which can reasonably be furnished by persons skilled in the art need not be specifically claimed where it is not the novel contribution of the inventors.") In the current case, it is the advantageous use of the TBA that is the novel contribution of the inventors.

The Examiner and the applicants are in agreement that the skill in this art is very high. Thus, there appears to be no disagreement with regard to *Wands factor* (f). Thus, there is ample precedent for expecting the efficacy of the current applicants' technology.

With regard to *Wands factor* (g), subsequent to the filing date of the subject invention, evidence of the efficacy of the technology set forth in the current invention has emerged. It turns out, in fact, that one needs to look no further than phages to find ample reason to believe that the applicants' unique system works as claimed in the subject application.

Lambda phage has two operators that govern which genes in its approximately 50,000 base pair genome are made and produced. Each operator (left operator and right operator) contains three binding sites that bind the cI and cro repressor proteins with different affinities. When the lambda

phage enters a bacterium, the phage initially makes cro repressors that bind to the operators and commit the phage to a lytic path. A sufficient number of copies of the phage (multiplicity of infection (MOI)) and a healthy infected cell (sufficient ATP) both are assessed by the virus through a host cell enzyme called Hfl. If the cell is healthy and the MOI is high enough, the phage makes a sufficient amount of cI to flip the lytic-lysogenic switch to lysogenic.

The cI protein acts as a TBA and binds the four binding sites within the operators of the phage genome as an octamer (Dodd *et al.*, 2001, 2003). Each dimer has a portion that recognizes binding sites within both left and right operators and assembly sequences that assemble the dimers into an octamer. The cI octamer directs the transcription of whatever genes are looped or "cradled" between one of the loops made by the assembly of the cI protein. Any protein placed in the "cradle" will be expressed in the stable lysogen.

Furthermore, the skilled artisan can readily place a gene in the "cradle" and have it selectively expressed or repressed (Langdon *et al.* 2001). This means that for a therapy delivered by a phage to be effective, the gene must only be able to be coded for by DNA, expressible in *E. coli* and be able to be exported out of *E. coli*. The coding requirement is trivial. Many proteins of therapeutic interest may be expressed in cell free systems that require compatibility with *E. coli* production because the ribosomes used in such systems are *E. coli* derived. Export systems for bacteria made proteins are well known. Although final therapeutic efficacy requires that the bacterially-produced and exported molecule bind to target cells and be imported into them, there are bacterial derived protein delivery systems that have been patented and used for this purpose (*e.g.* diphtheria toxin or exotoxin A targeting to cancer cells). For an example of the use of toxins to accomplish targeting and translocation, please see US patent 5,668,255.

In the context described above, the cI protein is analogous to a TBA of the subject invention. The cI protein assembles and binds to specific sites in both operators and in doing so loops the phage nucleic acid. This looping determines the direction of transcription and which genes are turned off and which genes are turned on. Any gene placed in the loop that is transcribed will be produced and a gene that is placed in the direction that is not transcribed will be turned off. If the SOS response of the infected cell is induced, genes in the silenced loop will be produced. In the case of naturally

occurring phage, genes produced when the switch is thrown towards lytic are directed towards the phage making copies of itself and exiting the cell, however, any gene may be placed in this loop as well, including antibiotic genes. In the case of naturally occurring phage, genes produced when the switch is thrown towards lytic are directed towards the phage making copies of itself and exiting the cell, however, any gene may be placed in this loop as well, including antibiotic genes.

The cI protein octamerization domain and the cro tetramerization domain can also be used as assembly sequences to mount any protein that binds to therapeutic sequences of interest in a way that produces looping. The cro and cI proteins are forgiving in that they readily accept other proteins and can act as carriers. In fact, the cro protein is often fused to other proteins in order to express difficult to express proteins. Proteins that bind nucleic acid targets present in cells and viruses may be readily fused. Please see the protein in attached Figure 1, a TBA that is the fusion of the cro protein and a rel binding domain. Many nucleic acid binding domains can be mounted onto the octamerization domain of cI to produce a TBA that will loop a set of tandem binding sites in the target genome where the tandem sites are presented on the same side of the helix and the centers of the binding sites are separated by a couple of turns of the DNA. While this process has more steps than ordering a complimentary nucleic acid for use in anti-sense work, it is no less enabled.

Control regions, whether bacterial, viral or cellular, are controlled by proteins that bind to specific sequences and assemble. In some cases the looping is tight (as is the case with an assembled, engineered, histone-like TBA) and in other cases the looping is larger (as in the case of lambda phage described above). For all transcriptional TBAs, transcription of a targeted gene is prevented in a direction by binding of the TBA or enabled in a direction by the binding of the TBA. Looping is an engineered consequence of TBA assembly and provides the transcriptional control.

The reviews of Verma and Andersen make the valid point that there are some limitations with using viruses as vectors for gene therapy and that in certain applications the viruses have had insufficient penetration and present a limitation on gene therapy. This is not true, however for all gene therapies or prophylactics that involve transgenic introduction of a therapeutic or prophylactic gene. An examination of the work of Lois, *et al* (2002) "Germline transmission and tissue-specific expression of transgenes delivered by lentiviral vectors" *Science* 1:295(5556):868-72.295:5556,

Chapman *et al* (2004) *Development* 132(5):935-940, and McGrew *et al.* (2004) "Efficient production of germline transgenic chickens using lentiviral vectors" *EMBO* Rep.:5(7):728-733, shows sufficient gene penetration of cells and tissues for gene therapy or prophylactic treatment with viruses as long as the treatment is applied to the germ cell or single cell embryo. Although there are significant ethical issues that would have to be resolved in order to apply a molecular lock to protect unborn generations from pathogens or pathogenic conditions using TBAs that are constitutively expressed by early introduction in humans, no such ethical barrier exists for bred animals. And, in any event, such ethical issues are not relevant to patentability.

With regard to the final *Wands factor*, the applicants respectfully submit that, to the extent that their claims can be considered broad, their application and invention are truly pioneering with a filing date going back to 1994. In this regard, it has not escaped the applicants' attention that this particular claim (or close variations thereof) has now been pending for over 5 years (with many previous office Actions) and enablement was not previously questioned. Therefore, while the applicants appreciate the Examiner's careful review of this case and the analysis of the *Wands* factors, they are also anxious to reach, and expedite, a favorable conclusion to this prosecution.

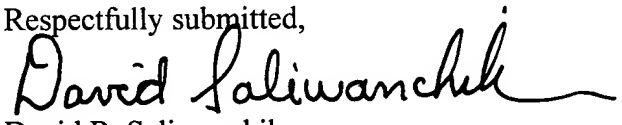
As noted above, the skilled artisan having the benefit of the current disclosure could readily practice the subject invention without undue experimentation. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

In view of the foregoing remarks above, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

The applicants also invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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Attachments: Figure 1
U.S. Patent No. 5,668,255
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Dodd, Ian B. *et al.* (2001) *Genes & Development* 15:3013-3022
Dodd, Ian B. *et al.* (2004) *Genes & Development* 18:344-354
Langdon, Robert C. *et al.* (2001) *Molecular Microbiology* 41(4):885-896